

## Abstract

### **The role of molecular cocrystals in drug development**

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The selection of the crystalline phases in a form of molecular cocrystals has become scientific challenge at the early stage of drug development of pharmaceutical formulations and in the late stage of synthesis and isolation of Active Pharmaceutical Ingredients (APIs) in desirable defined crystalline forms. Optimal crystal form of API interactively interrelates and impacts its aqueous solubility and dissolution rate that are benchmark for drug delivery and absorption determining the extent of its bioavailability and pharmacokinetics profile. Hence, determining the crystal structure and revealing the crystal packing forces and geometry of the API impact upon its physicochemical properties what it is a threshold for controlling the performance of the API. The range of crystal forms in which molecular cocrystals of APIs may exist are advantageous comparing to its polymorphs, salts, solvates and hydrates due to the vast number of potential coformers which extend the limited counterions for salt formation implying the existence of more complex intermolecular interactions based on different H-bonding patterns with API that lead to conformational changes and flexibility for crystal packing in process of cocrystallization.

Selected case-studies of cocrystallization screening reveals determined crystal structures of pharmaceutical cocrystals composed of APIs that belong to different pharmacotherapy and functional group classes, respectively. The case study underlines the crystal growth and the method of preparation for “drug-drug” type of pharmaceutical cocrystals wherein two different APIs cocrystallized in single crystal cell, and that represent new paradigm for approaching in development of the “fixed-doses” or “combo” pharmaceutical formulations. Preliminary results of the Structure-Activity Relationship study on the cocrystals composed of metformin with dichloroacetic acid indicates dual and complementary pharmacological activities of the two selected drug models for cocrystallization.